December 3, 2002

Laura H. Keller
Technical Contact
ExxonMobil Chemical Company
13501 Katy Freeway
Houston, TX 77079

Dear Ms. Keller:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Alkyl Alcohols C6-C13 Category posted on the ChemRTK HPV Challenge Program Web site on February 25, 2002. I commend ExxonMobil Chemical Company for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

ExxonMobil proposes to perform *in vivo* testing (mouse micronucleus assay) on alkyl alcohol C6 (CAS No. 68526-79-4) to complete the chromosomal aberrations endpoint for the category. In order to conform to the intent of EPA's October 14, 1999, letter to sponsors, which encourages the use of *in vitro* genotoxicity tests unless, for example, known chemical properties preclude their use, we ask sponsors to justify any planned *in vivo* chromosomal aberrations testing. The test plan states that such testing is planned in this case to provide comparability with the existing *in vivo* data for related substances. EPA understands the potential value of this approach, but believes that, given the consistent negative results in the available data as summarized in the test plan, in this case an *in vitro* test will provide adequate information.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that ExxonMobil advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
C6–C13 Alkyl Alcohols Category

SUMMARY OF EPA COMMENTS

The sponsor, ExxonMobil Company, submitted a test plan and robust summaries to EPA for C6 - C13 Alkyl Alcohols dated February 5, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 25, 2002.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Definition. The submitter needs to better support the proposed use of data on straight-chain analog alcohols to represent the sponsored branched chain alcohol mixtures.

2. Category Justification. The justification for grouping these branched alkyl alcohols appears appropriate. However, using data on analogs 1-hexanol and 1-dodecanol to support the category is not adequately justified for health effects endpoints. Additional information is needed on how a linear alcohol is a suitable analog for the branched category members; for example, whether its metabolism is similar to that of other members of the category. Available information on potential metabolites could be helpful.

3. Physicochemical Properties and Environmental Fate. (a) The submitted data for melting point are inadequate and testing is needed for this endpoint. Water solubility testing is needed for the mixtures lacking measured values; the data submitted for the C9-11 and C11-14 mixtures appear adequate, but additional experimental details need to be provided. EPA reserves judgment on the boiling point and vapor pressure endpoints pending submission of missing data elements. The submitted partition coefficient data are adequate for purposes of the HPV Challenge Program, although additional information needs to be provided on the compounds used for the estimated values. (b) EPA agrees with the test plan for the environmental fate endpoints.

4. Health Effects. (a) EPA recommends an *in vitro* test be conducted on alkyl alcohol C6 to complete chromosomal aberrations testing for the category. (b) EPA considers data submitted for repeated-dose and reproductive toxicity endpoints for C7-C9 alkyl alcohols to be inadequate. (c) As stated above, the submitter needs to provide additional information on the metabolism of 1-hexanol and 1-dodecanol and justify their use as analogs for branched chemicals. The submitter may also want to consider whether useful health effects data are available for potential metabolites of the category members and of related substances. (d) The submitter needs to address deficiencies in the robust summaries.

5. Ecological Effects. EPA considers the available data for acute toxicity in fish and invertebrates adequate for the purposes of the HPV Challenge Program. The submitter needs to conduct an algal study for a mid-range category member because the study submitted on isononyl alcohol is inadequate.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE C6 - C13 ALKYL ALCOHOLS CATEGORY HPV CHALLENGE SUBMISSION

Category Definition

The sponsor proposed a category of C6-C13 alkyl alcohols, which is represented by the structure RCH_2OH where R is a branched alkyl group having carbon numbers C5, C6, C7, C8, C9, C10, C11, or C12 as the main constituent. The specific substances sponsored are shown below.

CAS No. 68526-79-4: Hexanol, branched and linear

CAS No. 70914-20-4: Alcohols, C6-8, branched
CAS No. 68526-83-0: Alcohols, C7-9 iso, C8 rich (included to support category evaluation)
CAS No. 68526-84-1: Alcohols, C8-10 iso, C9 rich
CAS No. 68526-85-2: Alcohols, C9-11 iso, C10 rich
CAS No. 68526-86-3: Alcohols, C11-14 iso, C13 rich

Supporting information from the following chemicals was also provided:

CAS No. 111-27-3	1-Hexanol
CAS No. 104-76-7	2-Ethyl-1-hexanol
CAS No. 112-53-8	1-Dodecanol

The submitter needs to provide information on the mixture compositions, such as major constituents and typical percentages. It would be helpful for the submitter to state clearly that the category members are all primary alcohols. The test plan uses both RCOH and ROH as generic structures for the category, but it is clear from the production process description that the products must all be primary alcohols, RCH_2OH.

Category Justification

The submitter states that the members of the C_6-C_{13} alkyl alcohol category are very similar in physico chemical and toxicological properties, or that they vary in an incremental and predictable fashion within the category. Furthermore, similarities are suggested by common precursors and breakdown products resulting in similar metabolites (e.g., carboxylic acid). The justification for grouping these branched alkyl alcohols appears appropriate.

For health effects, the submitter proposes using data for 2-ethyl-1-hexanol, 1-hexanol and 1-dodecanol to support the category. No information is presented in the test plan on the metabolism of 1-hexanol and 1-dodecanol. Evidence that the metabolic pathway for these chemicals is similar to that of the branched category members will help to justify their use as analogs. The sponsor may also want to consider whether useful health effects data are available for potential metabolites of the category members, or of derivatives such as esters (for example, the HPV Challenge submission for Alkyl Acetates C6-C13 Category, posted on the ChemRTK Web site on February 7, 2001, may contain or cite useful information).

For ecological effects, the submitter's justification is adequate.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

The submitter states that physicochemical data for the major components of the mixtures in this category will be estimated using computer models such as EPIWIN. These data will be presented as ranges based on the chemical components selected to represent each alkyl alcohol product. Measured data for some of these endpoints will also be provided for selected alcohol products where readily available. No "selected alcohol products" were identified in the test plan by the submitter. The submitter also does not identify which mixtures will be tested. The submitter needs to address these omissions.

Melting point. Estimated melting point values are not reliable, especially for mixtures. Melting point testing using OECD TG 102 needs to be conducted on the sponsored chemical mixtures.

Boiling point and vapor pressure. Measured boiling point ranges and vapor pressures are provided for five of the HPV mixtures from MSDSs, but there is no documentation on the methods or the references. Comparison of the submitter's data to OECD Guidelines is not possible. EPA reserves judgment on the boiling point and vapor pressure endpoints pending submission of the missing data elements. Values from standard references are also acceptable if the original data source is cited.

Partition coefficient. The submitter's measured and estimated values appear to be adequate for the purposes of the HPV Challenge Program, although information needs to be provided on the compounds used for the EPIWIN estimates.

Water solubility. Measured water solubility data provided for "Alcohols C9-11, iso, C10 rich" and for "Alcohols C11-14, iso, C13 rich" appear adequate, but additional experimental details need to be reported. Values for the mixtures that lack measured values need to be determined experimentally (OECD TG 105).

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

EPA agrees with the submitter's approach to direct photolysis, stability in water, and biodegradation and that no additional testing is required for these endpoints.

Fugacity. The submitter plans to calculate the environmental distribution using the EPIWIN estimation software, and the test plan for this endpoint appears to be adequate for purposes of the HPV Challenge Program. While the HPV Challenge Program accepts Level I fugacity modeling to estimate transport/distribution values, EPA prefers values based on a Level III model as more realistic and useful for estimating a chemical's fate in the environment on a regional basis. Measured input values are preferred where appropriate.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data are available either on the category members or analogs for the acute toxicity endpoint for the purposes of the HPV Challenge Program. Adequate data are also available on an analog (2-ethyl-1-hexanol) for the genetic and developmental toxicity endpoints for alkyl alcohol C7-C9. Adequate data may exist for the developmental toxicity endpoint for alkyl alcohols C8-C10 and C9-C11 pending submission of missing robust summary information. EPA agrees with the submitter's proposal to conduct testing on alkyl alcohol C6 (CAS No. 68526-79-4) to address the chromosomal aberrations endpoint for the category and recommends an *in vitro* test be performed to satisfy the endpoint.

As stated above under Category Justification, EPA agrees that using data on appropriately chosen analogs is reasonable. The data on 2-ethyl-1-hexanol are applicable for addressing the health effects endpoints for alkyl alcohol C7-C9. However, EPA reserves judgement on the applicability of the submitted data on 1-hexanol and 1-dodecanol, which are linear alcohols proposed to address health effects endpoints for the branched category members (alkyl alcohols C6 and C11-C14). The submitter needs to supply adequate justification, such as discussion of metabolic pathways, to support their use as analogs and reduce the need for further testing to address the relevant endpoints. The submitter also needs to address deficiencies in robust summaries.

Repeated-Dose Toxicity. Alkyl alcohol C7-C9: The 90-day repeated-dose toxicity study on 2-ethyl-1-hexanol is inadequate because no information on specific organs that were weighed or examined for gross and microscopic pathology appears in the robust summaries (page 87of 163 of the IUCLID data set).

Reproductive Toxicity. Alkyl alcohol C7-C9: Although the reproductive toxicity endpoint can be addressed for the purposes of the Challenge program by documentation of the evaluation of reproductive organs in an existing 90-day repeated-dose toxicity study and an adequate developmental toxicity study, EPA considers that the 90-day repeated-dose toxicity study on 2-ethyl-1-hexanol is inadequate because no information on specific organs, especially reproductive organs, that were weighed or examined for gross and microscopic pathology appears in the robust summaries (page 102 of 163 of the IUCLID data set).

Developmental Toxicity. "[M]g/kg" in the summary table on page 12 of the Test Plan should be mg/kg/day.

Ecotoxicity (fish, invertebrates, and algae).

Fish and invertebrates. Available data are adequate for the purposes of the HPV Challenge Program. Although one submitted 24-hour invertebrate study is considered inadequate, the read-across approach

for all category members is considered satisfactory because adequate data were provided for an adjacent member of the series.

Algae. An algal test on a mid-range substance is necessary to adequately address this chemical category. The study submitted for isononyl alcohol is inadequate; the non-standard test protocol did not measure an appropriate EC50 value using acceptable methods.

Specific Comments on the Robust Summaries

Physicochemical Properties

Inconsistency in nomenclature was found for two of the sponsored substances in various sections of the test plan and robust summaries. CAS No. 68526-83-0 is described as "Alcohols, C7-9-iso-, C8-rich" (the correct 9th CI name for this CAS No.) and as "Alcohols C7-9 branched". These are two distinct substances with unique CAS numbers. CAS No. 68526-86-3 is reported both as "Alcohols, C11-14, iso, C13 rich" and "Alcohols, C11-14, iso, C12 rich." EPA could not locate a CAS number for the C12-rich substance. The submitter needs to clarify the identities of the sponsored and tested substances.

Boiling Point. The test report should include the following information: method used, chemical identity and impurities, estimated accuracy, and pressure of test.

Vapor Pressure. All data were measured at 100°C. The test report should include the following information: method used, chemical identity and impurities, and estimated accuracy.

Water Solubility. The submitter needs to provide additional experimental details for the measured values and identify the chemicals used in the EPIWIN calculations.

Partition Coefficient. The submitter needs to identify the chemicals used in the EPIWIN calculations.

Health Effects

Acute Toxicity. The submitter needs to provide the following missing information: age and body weight of the test animals, analytical methods, statistical methods, and confidence limits.

Genetic Toxicity. Alkyl alcohol C7-C9: For the Ames test, information missing from the IUCLID summary included the number of replicates per concentration, the source of the metabolic activation system, the analysis method and criteria, and the positive and negative results. For the *in vivo* cytogenicity chromosomal aberration assay in rats (ref. 144), the robust summary did not adequately describe the experimental design, time of exposure, and criteria for evaluating results. The *in vivo* dominant lethal assay summary (ref. 145) did not include the experimental design and the criteria for evaluating results.

Developmental Toxicity. The submitter needs to add quantitative data to all robust summaries.

Alkyl alcohol C7-C9: For the OECD TG 414 study on C7-C9 branched alcohols (EBSI 1994) on page 21 of the Robust Summaries, missing information includes visceral examination of fetuses and the purity of the test material.

Alkyl alcohol C8-C10: The submitter needs to provide the purity of the test material and percentage of the compositions of the chemicals for the studies conducted on isononylalcohol 1 and isononylalcohol 2 following OECD TG 414.

Alkyl alcohol C9-C11: The submitter needs to add the visceral examination of fetuses and the purity of the test material for the OECD TG 414 study on page 34 of 40 of the robust summaries.

Ecological Effects

Fish. For several of the studies the method, purity of test substance, and water hardness were not given.

Invertebrates. For several of the studies the method, purity of test substance, and water hardness were not given. In addition, the submitter needs to provide robust summaries, including all the data inputs, for the modeled (SAR) data discussed in the test plan.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.